Address. ... KS

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/096,593	6/12/98	O'Connor	SA-64559-3/RT.

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EXAMINER	
Lisa V. Cook	
ART UNIT	PAPER NUMBER
1641	9

DATE MAILED:

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) James Housel (Spe) (3) Lisa V. Cook

(2) Robin M. Silva (38,304) (4) Tom Meade (inventor)

Date of Interview 3/9/2000

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No If yes, brief description:

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: 18-28

Identification of prior art discussed: Inventor presentation; Robin Silva - discussion of inventions novelness over prior art. (103's)

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Claim language very broad possibly narrowing a re-writting recited claims would help further prosecution towards inventive concept.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

FORM PTOL-413 (REV.1-96)

Lisa. V. Cook 3/9/2000.

James C. Housel 3/9/00

Robin Silva 3/9/00

DETAILED ACTION

Election/Restriction

1. Currently, claims 1-19 are subject to restriction and election requirement. Applicant's Response to Office Action (paper #6), received 12 November 1999, paper # 7, is acknowledged. Election was made **without traverse** to prosecute the invention of Group III, claims 18 and 19. Claims 1-17, stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 18 and 19 have been amended. The following new claims have been added and will be prosecuted in the invention of Group III: claims 21, 22, 23, 24, 25, 26, 27, and 28.

2. Claims 18-28 are pending and currently under consideration.

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. The drawings in this application are objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948).

Specification

4. The specification is objected to because of the following informalities:

I. On page 16, System 7 at the top of the page is not identified.

Please label as system 7 or accordingly.

II. In Line 31, page 35 there appears to be something missing after the phrase "not limited to". Is this just incorrect spacing or was another structure intended to be recited. Please clarify.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 18-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 19 is indefinite because it is unclear as to what is encompassed within the phrase "processor". Is it applicant intent to mean a computer system for data analysis or an additional component in the electrode that will enhance the binding system?

B. In claims 18 and 20, the use of "self-assembled monolayer" is vague and indefinite because it is unclear if the monolayer is a component of the electrode that will be added to an existing electrode or is this layer a pre manufactured component of the electrode? Because the term is not defined in the specification the metes and bound can not be determined. What limitation if any is meant in this recitation? Please clarify.

C. Claim 22 is vague and indefinite in the use of the conductive oligomer formula. The intended composition of ***B*** has not been outlined. Further, ***D*** is not defined when g is 1. Is it applicants intent to mean any and all suitable compounds? These elements should be defined in their first instance. This initial explanation will convey intended meaning with subsequent abbreviations and applicants intended meaning. Please define.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

I. Claims 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vreeke et al (U.S.Patent#5,534,132) and O'Daly et al. (U.S.Patent#5,391,272) in view of Kossovsky et al. (U.S.Patent#5,585,646).

Vreeke et al. teach a biosensor for the detection of an affinity reaction. The sensor includes an electrode coated with a hydrogel. The hydrogel comprises a selective binding unit and redox species. The sensor is constructed by immobilizing a selective binding unit (SBU) into a three dimensional electron conducting redox hydrogel on a electrode (Column 2, Lines 25-30). Incubation of the affinity sensor with its complementary component leads to selective uptake of the complement from the solution. The selective binding agent serves to bring a redox enzyme labeled component into the hydrogel. In this way the electrode generates an

amperometric response via electrocatalytic reduction/oxidation of the enzyme substrate (Column 2, Lines 36-41). The selective binding unit may be any of the biological reagents that are able to form an affinity complex including biotin with avidin, antibody with antigen, single stranded DNA with opposite strand, and lectin with a sugar sequence (Column 3, Lines 51-56).

This invention is shown to be applicable in a competitive process. Here an unknown concentration of the selective binding agent, free in solution, is allowed to compete with the immobilized SBU for a limited peroxidase labeled complements. The current generated from oxidation/reduction of the enzyme is inversely related to the amount of unlabeled complement (Column 5, Lines 40-62).

In the method of this invention, the electrode is used to detect a redox enzyme labeled complement in a test sample. Avidin is immobilized at the electrode in the hydrogel and the conjugate biotin is labeled with a peroxidase redox enzyme (In example 1 biotin labeled horseradish peroxidase is employed). The affinity sensor is incubated in a solution containing the redox labeled complement. In Vreeke et al. binding of the complement immobilizes the redox enzyme in the hydrogel and this binding generates an electrical signal that is detected at the electrode (Column 5, Lines 17-27). In the case of peroxidase labels, the electron generation occurs when peroxidase is converted to hydrogen peroxide. The peroxidase enzyme is electroreduced at potentials of -0.35V (Ag/AgCl) and measured at +100 mV. This current is a function of the concentration of biotinylated peroxidase immobilized at the electrode by the selective binding unit.

The disclosed invention is disclosed to be a fast, compact, inexpensive, and separation free amperometric affinity sensor (column 2, Lines 25-27).

O'Daly et al. teach an electro-immunoassay for analyte detection in solution. The electro-immunosensor comprises an electrode coated with a colloidal gold absorbed anti-analyte antibody reversibly bound to an enzyme-analyte conjugate. The electrode may be any inert conducting material such as carbon, gold, silver, or platinum. These electrodes employ colloidal gold adsorbed enzymes deposited on the surface electrode surface coated with a compatible polymer. The polymer serves to stabilize the enzyme and provides a macroporous layer which allows access to the supporting electrolyte buffer components, electroactive mediator, and other compounds in solution (Column 12, Lines 28-51). Before, anti-analyte adsorption on the colloidal gold, it is usually desirable to coat the colloidal gold with a protein (e.g. bovine serum albumin or protein A). In certain embodiments, two or more anti-analyte antibodies may be adsorbed in the colloidal gold and deposited on the electrode surface. The enzyme is selected to provide a catalytic current in the presence of a suitable substrate. For example, horseradish peroxidase bound to a selected analyte and adsorbed onto the electrode surface-deposited anti-analyte antibody will generate a measurable current in the presence of hydrogen peroxide. Examples of enzymes that may be used in these assays include horseradish peroxidase, catalase, glucose oxidase, cholesterol oxidase, xanthine oxidase and similar enzymes. In preferred embodiments, a mediator which enhances electron transfer between the immobilized peroxidase and the electrode surface is included (Column 5, Lines 6-9). The invention is abatable to dual

analyte detection. In general a binding entity to the analyte or group of analytes one wishes to detect is apart of the reaction make-up. The binding entity is not limited to proteins and may be another type of macromolecule whether naturally occurring, recombinant or synthetic. When suitably combined with a reference and working electrode, the electrode/receptor/analyte/enzyme complex in the presence of a substrate for the enzyme causes a measurable electrical current. Redox amplification occurs because a single redox enzyme-labeled antibody recognition results in shuttling of large numbers of electrons between the enzymes and the electrode.

Vreeke et al. and O'Daly et al. differ from the instant invention in failing to teach a self - assembled monolayer and a conductive oligomer spacer in their device designs.

Kossovsky et al. disclose improved bioelectronics devices in comprising a layer of a polyhydroxy oligomer that is spaced between the surface of a semiconductive material (applicants monolayer) and a electronically active biochemical molecule (applicants binding ligand) which is bound to the semiconductive surface of an electronic device (applicants electrode). The layer of polyhydroxy oligomer functions as a biochemical stabilization layer to prevent denaturization of the electronically active biochemical molecule (Abstract). The stabilization layer is made up of one or more polyhydroxy oligomers. Exemplary polyhydroxy oligomers include carbohydrates, carbohydrate derivatives, and other macro molecules with carbohydrate like components.

Kossovsky et al. further teach that the surface modification concept and the electron donor-acceptor concept can be combined at the semiconductor surface and utilized in various methods. Specifically cited is the method of Colvin et al.(Column 4, Lines 12-25). Colvin et al. Construct devices by attaching semiconductor nanocrystals to metal surfaces using self assembled monolayers as bridging compounds.

Vreeke et al., O'Daly et al., and Skotheim et al. are analogous art because they are from the same field of endeavor, all three inventions teach the fabrication of electrochemical biosensors.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the self assembled monolayers taught by Kossovsky et al. in either method of Vreeke et al. or the method of O'Daly et al. to perform analyte detection in an affinity assay system because such self assembled monolayers and oligomer spacers as taught by Kossovsky et al. are well known in the art. A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such materials, because Kossovsky et al. disclosed that the use of self assembled monolayers allows the molecules to be held in a specific orientation with respect to the metal and are applicable in many system designs (Column 4, Lines 12-25).

> recent advances have extended self assembled monolayers beyond the prototype gold/thiol systems. Fatty acids on aluminum, silanes on silicon, isonitriles on platinum and rigid phosphates on metals are all examples.

Kossovsky et al. also teach the use of the any denaturization of the biochemical material which might be caused by the semiconductor material is eliminated or substantially reduced by placing the stabilization layer of polyhydroxy oligomers between the biochemical material and the semiconductor (Column 7, Lines 13-18).

II. Claims 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al (U.S.Patent#5,972,199) and Skotheim et al. (U.S.Patent#5,089,112) in view of Kossovsky et al. (U.S.Patent#5,585,646).

Heller et al. disclose a sensor for detecting and measuring analytes in biological fluids. The sensor include at least two enzymes, a thermostable peroxidase, such as soybean peroxidase, and a peroxidase-generating enzyme. The sensor measures the concentration of hydrogen peroxide utilizing a peroxidase enzyme immobilized in a redox hydrogel coated on an electrode. The sensor also includes a hydrogen peroxide-generating second enzyme. The redox centers of the peroxide-generating enzyme are electrically insulated from the electrode, from the thermostable peroxidase, and from the redox hydrogel. The peroxide-generating enzyme catalyzes the reaction of a biochemical analyte (e.g. glucose or lactate) with molecular oxygen. In the oxidation reaction, oxygen is reduced to hydrogen peroxide. Sensors of this invention have one or more working electrodes and one or more counter, reference, and/or counter/reference electrodes. See Column 5, Lines 47-50.

Skotheim et al. disclose an electrochemical enzyme biosensor which detects selected components in liquid mixtures. The biosensor entails a polymer backbone, a mediator compound, and enzymes specific the analyte for detection. The preferred enzymes are non-oxygen specific flavo-protein or quino-protein enzymes, in particular glucose oxidase and glucose dehydrogenase. Other favo-protein enzymes include aldehyde oxidase for aldehyde detection, glycolate oxidase for glycolate detection, choline oxidase for choline detection, etc (Column 5, lines 1-14). The electrodes are coated with a siloxane-ferrocene polymer/glucose oxidase mixture and the presence of the analyte in a solution produces a measurable potential. In general, the redox compounds which can be covalently attached to the polymer have redox potentials that range from -0.2 to 0.6 V vs. Saturated Calomel electrode (SCE)- Column 4, Lines 53-57.

Heller et al. and Skotheim et al. differ from the instant invention in failing to teach a self - assembled monolayer and a conductive oligomer spacer in their device designs.

Kossovsky et al. disclose improved bioelectronics devices in comprising a layer of a polyhydroxy oligomer that is spaced between the surface of a semiconductive material (applicants monolayer) and a electronically active biochemical molecule (applicants binding ligand) which is bound to the semiconductive surface of an electronic device (applicants electrode). The layer of polyhydroxy oligomer functions as a biochemical stabilization layer to prevent denaturization of the electronically active biochemical molecule (Abstract). The stabilization layer is made up of one or more polyhydroxy oligomers. Exemplary polyhydroxy

oligomers include carbohydrates, carbohydrate derivatives, and other macro molecules with carbohydrate like components.

Kossovsky et al. further teach that the surface modification concept and the electron donor-acceptor concept can be combined at the semiconductor surface and utilized in various methods. Specifically cited is the method of Colvin et al.(Column 4, Lines 12-25). Colvin et al. Construct devices by attaching semiconductor nanocrystals to metal surfaces using self assembled monolayers as bridging compounds.

Heller et al., Skotheim et al., and Kossovsky et al. are analogous art because they are from the same field of endeavor, all three inventions teach analyte detection employing electrochemical biosensors.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the self assembled monolayers taught by Kossovsky et al. in either method of Vreeke et al. or the method of O'Daly et al. to perform analyte detection in an affinity assay system because such self assembled monolayers and oligomer spacers as taught by Kossovsky et al. are well known in the art. A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such materials, because Kossovsky et al. disclosed that the use of self assembled monolayers allows the molecules to be held in a specific orientation with respect to the metal and are applicable in many system designs (Column 4, Lines 12-25).

> recent advances have extended self assembled monolayers beyond the prototype gold/thiol systems. Fatty acids on aluminum, silanes on silicon, isonitriles on platinum and rigid phosphates on metals are all examples.

Kossovsky et al. also teach the use of the any denaturization of the biochemical material which might be caused by the semiconductor material is eliminated or substantially reduced by placing the stabilization layer of polyhydroxy oligomers between the biochemical material and the semiconductor (Column 7, Lines 13-18).

III. Claims 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delamarche et al. (American Chemical Society, Languir 1996, Vol.12, pages 1997-2006) in view of Kossovsky et al. (U.S.Patent#5,585,646) and in further view of Gafni et al. (Chem. Eur. J. 1996, Vol.2, No.7).

Delamarche et al. disclose a system for the covalent attachment of proteins. A self assembled monolayer is prepared by adsorbing a disulfide on gold. Functional groups at the termini of the self-assembled monolayer are converted into a benzophenone derivative. The photoimmobilized antibodies cover the surface (e.g. IgG). Thus allowing for protein binding. Delamarche et al. Vreeke et al. and O'Daly et al. differ from the instant invention in failing to teach this sytsems ultility an oligomer spacer in voltage systems.

See prior discussion of Kossovsky et al. (U.S.Patent#5,585,646). *(In 103 rejections I and II.)*

Gafni et al. teach novel self-assembled monolayers that are characterized by AC-Impedence spectroscopy. The gold elctrodes serves as a support for the self-assembled monolayer as well as the source of electrochemical signal required to probe the binding of ions. Ion binding was shown to based upon selective ligand binding and this binding allowed electron transfer that was monitored by voltammetry. A detailed analysis of the alternating current (AC) impedence spectra is presented for monolayers on gold electrodes, where the impedence data are fitted to an equivalent circuit model. It is hown that the Ac response in a wide frequency range can be used to probe ion binding and release in monolayer systems on electrodes (Abstract).

Delamarche et al., Kossovsky et al., and Gafni et al. are analogous art because they are from the same field of endeavor, all three inventions teach analyte detection employing self assembled monolayers.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the voltage detection system taught by Gafni et al. in the method of Delamarche et al. to detect proteins because such altered current (AC) devices as taught by Gafni et al. are well known in the art. A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such devices, because these systems were taught to have the following improvements over the previous systems:(See Gafni et al. page 760, Column 1, Final paragraph) The advantages of AC-impedence spectroscopy are (1) analysis in a wide frequency range which provides a complete picture of the elctrical properties, (2) minimizes disturbance to the monolayer and (3) allow for exponential dependency.

7. For reasons aforementioned, no claims are allowed.

Remarks

8. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Meade et al. (U.S.Patent#5,824,473) disclose selective coavalent modification of nucleic acids with redox active moieties. The invention repesents a series of new derivatives that ar biomolecular templates capable of transferring electrons over very large distances at extremely fast rates.

B. Taylor, CK (The university of Texas at Austin, Vol.59/06-B, 1998, page 2726) disclose glucose or lactate oxidase employed in a redox polymer formed on vitreous carbon electrode surfaces. The redox potential of the hydrogel was -69mV (SCE) for polyvinyl imidazole, +35mV (SCE) for polyvinyl pyridine, and +25mV (SCE) for acrylonitrile. Their glucose electrooxidation current reached a plateau at +50mV (SCE), +150mV(SCE), and +50mV (SCE) respectively. Urate and acetaminophen were not electrooxidized at this potential at rates that would interfere with the glucose and lactate assays.

C. Rauh (U.S. Patent#5,922,183) teach metal oxide matrix biosensors utilized in biological molecule detection. The system can be employed in amperometric and potentiometric sensing.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook

Art Unit 1641

CM1-7D16

March 6, 2000